ORIGINAL ARTICLE

Clinical and bacteriological efficacy of the ketolide telithromycin against isolates of key respiratory pathogens: a pooled analysis of phase III studies

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ABSTRACT

A pooled analysis of data from 13 phase III studies of telithromycin in the treatment of community-acquired pneumonia, acute exacerbations of chronic bronchitis, acute sinusitis or group A β-haemolytic streptococcal pharyngitis and tonsillitis was undertaken. Causative key respiratory tract pathogens (*Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis*, *Staphylococcus aureus* and *Streptococcus pyogenes*) were isolated at entry to the studies from cultures of relevant respiratory samples and tested for their susceptibility to telithromycin, penicillin and macrolides (erythromycin A). The combined clinical and bacteriological efficacy of telithromycin at the post-therapy, test-of-cure visit (days 17–24) was assessed in patients from whom a microbiologically evaluable pathogen was isolated at entry. More than 98% of key respiratory pathogens isolated, including penicillin G- and macrolide (erythromycin A)-resistant strains of *S. pneumoniae*, demonstrated full or intermediate susceptibility to telithromycin *in vitro* at the breakpoints of ≤1.0 mg/L (susceptible) and 2.0 mg/L (intermediate) used for the purpose of evaluating the susceptibility of isolates recovered during the clinical trials. Treatment with telithromycin 800 mg once-daily for 5, 7 or 7–10 days resulted in high rates of clinical cure (88.5%) and a satisfactory bacteriological outcome (88.9%), similar to the figures seen with comparator antibacterial agents. Clinical cure and eradication rates were good for all key respiratory pathogens, including penicillin G- and macrolide (erythromycin A)-resistant *S. pneumoniae*. The results suggest that telithromycin will provide effective empirical therapy for community-acquired upper and lower respiratory tract infections.

Keywords Telithromycin, respiratory pathogens, clinical efficacy, bacteriological efficacy

Original Submission: 27 May 2002; **Revised Submission:** 16 December 2002; **Accepted:** 12 February 2003

Clin Microbiol Infect 2004; 10: 27–36

INTRODUCTION

Community-acquired respiratory tract infections (RTIs), namely community-acquired pneumonia (CAP), acute exacerbations of chronic bronchitis (AECB), acute sinusitis, and pharyngitis and tonsillitis, account for considerable morbidity and can result in serious complications, including death, if left untreated [1–4]. Successful management of patients with community-acquired RTIs therefore dictates the prompt use of empirical therapy with an antibacterial that provides good coverage of all key respiratory pathogens likely to be encountered. However, a global pattern of decreasing susceptibility and/or increasing emergence of resistance has become apparent in recent years, and this is starting to have an impact on the choice of antibacterial agent. For example, key respiratory pathogens such as *Streptococcus pneumoniae* are becoming resistant to β-lactams and/or macrolides [5,6], while macrolide resistance among *Streptococcus pyogenes* is increasing in many countries [7–10]. Such resistance threatens the clinical usefulness of many of the currently used antibacterial agents in the treatment of community-acquired RTIs [11–14], and highlights the need for additional agents that retain activity against resistant pathogens, and which also have a low potential to induce—or select for—resistant strains.

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Telithromycin is the first of a new class of antibacterial agents—the ketolides—developed specifically for the treatment of community-acquired upper and lower RTIs [15], including those caused by pathogens resistant to commonly used antibiotics. Numerous in-vitro studies have shown that telithromycin has excellent activity against common respiratory pathogens such as *S. pneumoniae*, including isolates that are resistant to penicillin G and/or macrolides (erythromycin A) *S. pyogenes* and *Moraxella catarrhalis*, and good activity against *Haemophilus influenzae* [16–26]. Moreover, telithromycin is active against atypical and intracellular respiratory pathogens such as *Mycoplasma pneumoniae*, *Chlamydophila* (*Chlamydia*) *pneumoniae* and *Legionella pneumophila* [27–30], which are being identified with increasing frequency in patients with CAP [31] as a result of improved diagnostic techniques. The well-balanced antibacterial spectrum of telithromycin is accompanied by a low potential to induce—or select for—resistance [32,33], a profile that highlights the potential utility of this new agent for the treatment of community-acquired RTIs.

The efficacy and safety of telithromycin, at an oral dose of 800 mg once-daily, have been confirmed in 13 phase III clinical trials in patients with community-acquired upper and lower RTIs, most of which included the current antibacterial 'standard of care' as comparator [15,34–43]. The present paper provides a pooled analysis of these studies in terms of the clinical and bacteriological efficacy of telithromycin, with a particular focus on activity against key respiratory tract pathogens.

MATERIALS AND METHODS

Patients and study design

The study population comprised adult patients (aged ≥18 years) with a confirmed diagnosis of CAP, AECB, acute sinusitis, or group A β-haemolytic streptococcal pharyngitis/tonsillitis, who took part in one of 13 multicentre phase III studies (Table 1). Adolescents (aged 13–18 years) were also included in the pharyngitis and tonsillitis studies.

The CAP studies included patients with a diagnosis based on X-ray findings and the presence of at least two of the following clinical signs and symptoms: cough, production of purulent sputum, Gram-stain findings consistent with a respiratory pathogen, auscultatory findings, dyspnoea or tachypnoea, fever, and elevated total peripheral white blood cell count. The AECB studies included patients with a documented history of chronic bronchitis who presented with an episode of

Table 1. Summary of the 13 phase III clinical trials with telithromycin included in the pooled analysis

Indication	No. of trials (study no.)	Telithromycin dosage (*n*)	Comparator dosage (*n*)	Reference
CAP	1 (3001)	800 mg once-daily for 10 days (199)	AMX 1000 mg three times daily for 10 days (205)	37
	1 (3006)	800 mg once-daily for 10 days (204)	CLA 500 mg twice-daily for 10 days (212)	40
	1 (3009)	800 mg once-daily for 7–10 days (100)	TVA 200 mg once-daily for 7–10 days (104)	15
	2 (3000; 3009OL)	800 mg once-daily for 7–10 days (452)	–	36,43
	1 (3010)	800 mg once-daily for 7 days (418)	–	41
AECB	1 (3003)	800 mg once-daily for 5 days (160)	AUG 500/125 mg three times daily for 10 days (160)	35
	1 (3007)	800 mg once-daily for 5 days (182)	CXM 500 mg twice-daily for 10 days (191)	15
Acute sinusitis	1 (3002)	800 mg once-daily for 5 or 10 days (335)	–	39
	1 (3005)	800 mg once-daily for 5 or 10 days (405)	AUG 500/125 mg three times daily for 10 days (202)	15
	1 (3011)	800 mg once-daily for 5 days (240)	CXM 250 mg twice-daily for 10 days (116)	34
Pharyngitis and tonsillitis	1 (3004)	800 mg once-daily for 5 days (198)	PEN 500 mg three times daily for 10 days (197)	38
	1 (3008)	800 mg once-daily for 5 days (232)	CLA 250 mg twice-daily for 10 days (231)	42

AECB, acute exacerbation of chronic bronchitis; CAP, community-acquired pneumonia; AMX, amoxycillin; AUG, amoxycillin–clavulanate; CLA, clarithromycin; CXM, cefuroxime axetil; PEN, penicillin V (phenoxymethylpenicillin); TVA, trovafloxacin; *n* = number of patients (modified intent-to-treat population).

AECB presumed to be caused by bacterial infection. Clinical diagnosis of AECB was based on the presence of at least two of the following signs and symptoms: increased sputum volume, increased sputum purulence, and increased cough or dyspnoea. For the acute sinusitis studies, inclusion criteria included clinical symptoms of acute sinusitis of < 28 days' duration and radiological evidence of total sinus opacity and/or air–fluid levels. Patients with clinical signs and symptoms of acute pharyngitis and tonsillitis were eligible for inclusion if they had either a positive streptococcal antigen test from a throat swab or a positive throat culture for group A β-haemolytic streptococcus. Written informed consent was obtained from all patients or their parents/guardians before any study-related procedures. Human experimentation guidelines of each participating study centre were followed in the conduct of clinical research.

Study treatments

Eligible patients received oral telithromycin 800 mg once daily for 7 or 7–10 days (CAP), 5 or 10 days (acute sinusitis), or 5 days (AECB, pharyngitis and tonsillitis) (Table 1). Various oral antibacterials were included as comparators, depending on the indication. In the CAP studies, the comparators were amoxycillin 1000 mg three times daily, clarithromycin 500 mg twice-daily, and trovafloxacin 200 mg once-daily. Amoxycillin–clavulanate 500 + 125 mg three times daily, and cefuroxime axetil 500 mg twice-daily, were chosen as comparators in the AECB studies. In the acute sinusitis studies, the comparators were amoxycillin–clavulanate 500 + 125 mg three times daily, and cefuroxime axetil 250 mg twice-daily. Finally, comparator antibacterials in the pharyngitis and tonsillitis studies were penicillin V (phenoxymethylpenicillin) 500 mg three times daily, and clarithromycin 250 mg twice-daily. All comparator antibacterials were given as a 10-day course, with the exception of trovafloxacin, which was given as a 7–10-day course. Compliance was assessed by unused tablet counts at the on-therapy and post-therapy visits.

Susceptibility testing

Causative key respiratory tract pathogens (*S. pneumoniae*, *H. influenzae*, *M. catarrhalis*, *Staphylococcus aureus* and *S. pyogenes*) were isolated at entry to the study from cultures of relevant respiratory samples, namely sputum (CAP and AECB studies), sinus aspirates obtained by sinus puncture or endoscopy (acute sinusitis studies) or throat swabs (pharyngitis and tonsillitis studies, in which swabs were tested for streptococcal antigen before bacteriological culture was performed), or from blood (CAP). All isolated bacterial pathogens were categorised by the investigator as either causative, contaminant, colonising or part of the normal oral flora (mixed flora). A bacterial pathogen was considered to be causative if the isolate(s) obtained at the initial visit was from an appropriate sample (as defined above) and was identified as an organism that is generally accepted as pathogenic for the indication under study. Susceptibility testing of clinical isolates was performed using disk diffusion methods at each investigator's local laboratory. Subcultures of primary isolates were subsequently retested at a central laboratory (Clinical Microbiology Institute, Wilsonville, OR, USA, or GR Micro Ltd, London, UK) by disk diffusion and for MICs by National Committee for Clinical Laboratory Standards methodology [44]. Susceptibility to telithromycin was assessed according to the following MIC breakpoints (susceptible, intermediate and resistant, respectively) as used for the purpose of evaluating isolates recovered during the clinical trials: streptococci and staphylococci, ≤ 1.0, 2.0 and ≥ 4.0 mg/L; *Haemophilus* spp., ≤ 2.0, 4.0 and ≥ 8.0 mg/L. PCR analysis for the presence of *erm* and *mef* sequences was performed on isolates of *S. pneumoniae* and *S. pyogenes* resistant to macrolides (erythromycin A) [45].

Assessment of clinical and bacteriological outcome

The primary outcome was the combined clinical and bacteriological efficacy at the post-therapy, test-of-cure visit, i.e., days 17–24 for CAP, AECB and acute sinusitis studies, and days 16–23 for the pharyngitis and tonsillitis studies. Clinical cure was defined as clinical improvement or return to the preinfection state, while bacteriological outcome was classed as satisfactory if there was eradication or presumed eradication of the causative pathogen. Analyses were performed for the bacteriologically evaluable, modified intent-to-treat population, i.e., all patients who had a confirmed diagnosis of the studied indication and received at least one dose of study medication, with a pre-therapy bacteriological sample containing at least one causative pathogen. Those without major protocol violations were included in the bacteriological per-protocol (PP) population for analysis of bacteriological outcome. All analyses were completed descriptively.

RESULTS

The pooled phase III population comprised 3125 patients treated with telithromycin. Key demographic characteristics, across indications, are shown in Table 2.

Table 2. Key demographic characteristics of telithromycin-treated patients across indications (modified intent-to-treat population)

	CAP	AECB	Acute sinusitis	Pharyngitis and tonsillitis
Total no. of patients	1373	342	980	430
Sex, male/female	779/594	178/164	442/538	171/259
Mean age (years)	44.6	56.3	39.6	31.6
Patients aged ≥ 65 years (%)	196 (14.3)	114 (33.3)	48 (4.9)	2 (0.5)

AECB, acute exacerbation of chronic bronchitis; CAP, community-acquired pneumonia; n = number of patients.

In-vitro susceptibility

In total, 1894 causative pathogens isolated from respiratory samples and blood cultures at baseline were tested for susceptibility to telithromycin. With application of susceptibility breakpoints as defined in the clinical trials, >88% of all pathogens were of full or intermediate susceptibility, with 81.4% of all isolates demonstrating full susceptibility to telithromycin. Most isolates that were not susceptible to telithromycin were not key causative pathogens of community-acquired RTIs (*H. parainfluenzae*, *Klebsiella pneumoniae*, *Escherichia coli* and *Pseudomonas aeruginosa*).

The causative pathogens most frequently isolated from respiratory or blood samples were *S. pneumoniae*, *H. influenzae*, *M. catarrhalis*, *S. pyogenes* and *Staph. aureus* (Table 3). Overall, >98% of these key respiratory pathogens were either susceptible or of intermediate susceptibility to telithromycin when breakpoints used for the purpose of evaluating the susceptibility of isolates recovered during the clinical trials were applied. All isolates of *S. pneumoniae*, including those resistant to penicillin G or the macrolides (erythromycin A), were of full or intermediate susceptibility (Table 4). Two *S. pneumoniae* isolates of intermediate susceptibility to telithromycin were also resistant to penicillin G and erythromycin A. In total, 590 (99.3%) of 594 isolates of *S. pyogenes* were fully susceptible to telithromycin; the four isolates that were resistant were all *ermB* positive. Eighty-seven of 89 *Staph. aureus* isolates were fully susceptible to telithromycin; the two isolates that were resistant to telithromycin were also cross-resistant to erythromycin A. All isolates of *M. catarrhalis* were inhibited by telithromycin ≤1 mg/L. Most (239 (69.9%) of 342) *H. influenzae* isolates were also susceptible to telithromycin ≤2 mg/L, while a further 88 (25.7%) *H. influenzae* isolates were inhibited by telithromycin ≤4 mg/L (95.6% in total).

Of 69 pathogens isolated from blood cultures in patients with CAP, 68 (98.6%) were fully susceptible to telithromycin. These comprised 61 isolates of *S. pneumoniae*, including penicillin G- and macrolide (erythromycin A)-resistant strains, one isolate of *Staph. aureus*, two isolates of *viridans* group streptococci, two isolates of *Staph. haemolyticus*, one isolate of *Staph. hyicus*, and one isolate of *Bacillus cereus*. (Note: viridans group streptococci, *Staph. haemolyticus*, *Staph. hyicus* and *Bacillus cereus*, although not generally considered to be causative of community-acquired RTIs, were assessed by the investigators as causative pathogens. These are most often interpreted as skin contaminants when recovered from blood cultures.) Only one organism isolated from blood—*E. coli*—was resistant to telithromycin (as expected, based on the antibacterial spectrum of this agent).

Table 3. Causative pathogens isolated at entry from respiratory/blood cultures from patients with community-acquired respiratory tract infections

Pathogen	Number (%) of isolates
Community-acquired pneumonia	
Streptococcus pneumoniae	250 (33.7)
Haemophilus influenzae	197 (26.6)
Moraxella catarrhalis	45 (6.1)
Staphylococcus aureus	39 (5.3)
Klebsiella pneumoniae	23 (3.1)
Other[a]	187 (25.2)
Total no. of isolates	741
Acute exacerbations of chronic bronchitis	
Haemophilus influenzae	59 (39.6)
Streptococcus pneumoniae	28 (18.8)
Moraxella catarrhalis	29 (19.5)
Staphylococcus aureus	5 (3.4)
Klebsiella pneumoniae	2 (1.3)
Other[b]	26 (17.4)
Total no. of isolates	149
Acute maxillary sinusitis	
Streptococcus pneumoniae	116 (27.6)
Haemophilus influenzae	88 (21.0)
Staphylococcus aureus	45 (10.7)
Moraxella catarrhalis	30 (7.1)
Klebsiella pneumoniae	3 (0.7)
Streptococcus pyogenes	2 (0.5)
Other[c]	136 (32.4)
Total no. of isolates	420
Pharyngitis and tonsillitis	
Streptococcus pyogenes	594 (100)
Total no. of isolates	594

[a]Including *Haemophilus parainfluenzae*, *Escherichia coli*, *Klebsiella pneumoniae* and *Pseudomonas aeruginosa*.
[b]Including *H. parainfluenzae*, *E. coli* and *Pseudomonas* spp.
[c]Including *H. parainfluenzae*, group C and G β-haemolytic streptococci, coagulase-negative staphylococci, *Bacteroides* spp., *E. coli* and *P. aeruginosa*.

Clinical and bacteriological efficacy

Combined clinical cure rates and bacteriological outcome at the post-therapy, test-of-cure visit for telithromycin and comparator modified intent-to-treat populations are summarised in Table 5.

Table 4. Susceptibility[a] to telithromycin of key respiratory pathogens isolated from respiratory or blood samples

Pathogen	No. of isolates	Susceptible *n* (%)	Intermediate *n* (%)	Resistant *n* (%)
Total key pathogens	1523	1412 (92.7)	90 (5.9)	21 (1.4)
Streptococcus pneumoniae				
All isolates	394	392 (99.5)	2 (0.5)	–
Penicillin G resistant[b]	47	45 (95.7)	2 (4.3)[d]	–
Erythromycin A resistant[c]	58	56 (96.6)	2 (3.4)[d]	–
Haemophilus influenzae				
All isolates	342	239 (69.9)	88 (25.7)	15 (4.4)
β-Lactamase positive	63	49 (77.8)	13 (20.6)	1 (1.6)
Staphylococcus aureus	89	87 (97.8)	–	2 (2.2)
Streptococcus pyogenes	594	590 (99.3)	–	4 (0.7)

[a]Breakpoints as defined in the clinical study protocols (susceptible, intermediate and resistant) were adopted as follows: streptococci and staphylococci, ≤ 1.0 mg/L, 2.0 mg/L and ≥ 4.0 mg/L; *Haemophilus influenzae*, ≤ 2.0 mg/L, 4.0 mg/L and ≥ 8.0 mg/L; no breakpoints were available for *Moraxella catarrhalis*, but all isolates were inhibited by ≤ 1 mg/L.
[b]MIC ≥ 2.0 mg/L.
[c]MIC ≥ 1.0 mg/L.
[d]Isolates were both penicillin and erythromycin resistant.

Table 5. Rates of clinical cure and satisfactory bacteriological outcome at the post-therapy, test-of-cure visit (bacteriologically evaluable modified intent-to-treat population)

Antibacterial	Clinical cure, *n/N* (%)[a]	Satisfactory bacteriological outcome, *n/N* (%)[b]
Telithromycin	1282/1448 (88.5)	1265/1423 (88.9)
5-day course[c,d]	584/670 (87.2)	566/648 (87.3)
7–10-day course[c,e]	698/778 (89.7)	699/775 (90.2)
Clarithromycin[e]	186/205 (90.7)	175/195 (89.7)
Trovafloxacin[e]	39/44 (88.6)	43/45 (95.6)
Amoxycillin[e]	53/62 (85.5)	52/61 (85.2)
Cefuroxime axetil[c,d]	83/105 (79.0)	84/105 (80.0)
Amoxycillin–clavulanate[c,d]	45/59 (76.3)	44/55 (80.0)
Penicillin V[f]	129/140 (92.1)	119/135 (88.1)

[a]Clinical improvement or return to preinfection state.
[b]Documented or presumed eradication of the pathogen from respiratory secretions and/or blood cultures.
[c]Acute sinusitis.
[d]Acute exacerbations of chronic bronchitis.
[e]Community-acquired pneumonia.
[f]Tonsillitis/pharyngitis.

Treatment with telithromycin for 5 or 7–10 days resulted in high rates of clinical cure and satisfactory bacteriological outcome that were similar to those seen with the comparator antibacterial agents. Overall, 88.5% of telithromycin-treated patients were clinically cured and 88.9% of causative pathogens were eradicated or presumed to be eradicated. For the comparator agents, the rates of clinical cure in the various conditions ranged from 76.3% (for amoxycillin–clavulanate with acute sinusitis and AECB combined) to 92.1% (for penicillin V with tonsillitis and pharyngitis), while eradication rates ranged from 80.0% (amoxycillin–clavulanate and cefuroxime axetil) to 95.6% (trovafloxacin).

For telithromycin-treated patients, the PP clinical cure and bacteriological eradication rates at the post-therapy, test-of-cure visit for key causative pathogens, according to telithromycin susceptibility, are shown in Table 6. Overall, clinical cure and eradication rates were good for all key respiratory pathogens, including penicillin G- and macrolide (erythromycin A)-resistant *S. pneumoniae*. Clinical efficacy in infections caused by erythromycin A-resistant *S. pneumoniae* was comparable with that observed for all *S. pneu-*

Table 6. Clinical cure and eradication rates in telithromycin-treated patients, by key causative pathogen and according to telithromycin MIC[a], at the post-therapy, test-of-cure visit (bacteriologically evaluable per-protocol population)

Pathogen and telithromycin MIC	No. of isolates	Clinical cure (%)	Eradication (%)
Streptococcus pneumoniae			
All isolates	245	93.1	94.3
MIC ≤ 1.0 mg/L	244	93.0	94.3
MIC 2.0 mg/L	1	100	100
MIC ≥ 4.0 mg/L	0	–	–
Streptococcus pneumoniae (PEN-R)			
All isolates	29	82.8	82.8
MIC ≤ 1.0 mg/L	28	82.1	82.1
MIC 2.0 mg/L	1[b]	100	100
MIC ≥ 4.0 mg/L	0	–	–
Streptococcus pneumoniae (ERY-R)			
All isolates	37	83.8	83.8
MIC ≤ 1.0 mg/L	36	83.3	83.3
MIC 2.0 mg/L	1[b]	100	100
MIC ≥ 4.0 mg/L	0	–	–
Haemophilus influenzae			
All isolates	178	87.1	84.3
MIC ≤ 2.0 mg/L	129	85.3	82.2
MIC 4.0 mg/L	41	95.1	92.7
MIC ≥ 8.0 mg/L	8	75.0	75.0
Moraxella catarrhalis			
All isolates	51	92.2	94.1
Staphylococcus aureus			
All isolates	39	87.2	89.7
MIC ≤ 1.0 mg/L	39	87.2	89.7
MIC 2.0 mg/L	0	–	–
MIC ≥ 4.0 mg/L	0	–	–
Streptococcus pyogenes			
All isolates	249[c]	93.2	88.4
MIC ≤ 1.0 mg/L	247	93.1	88.3
MIC 2.0 mg/L	0	–	–
MIC ≥ 4.0 mg/L	0	–	–
Streptococcus pyogenes (ERY-R)			
All isolates	11	90.9	27.3
MIC ≤ 1.0 mg/L	11	90.9	27.3
MIC 2.0 mg/L	0	–	–
MIC ≥ 4.0 mg/L	0	–	–

[a]Breakpoints as defined in the clinical study protocols.
[b]Isolate was both penicillin G and erythromycin A resistant.
[c]MICs were not determined for two isolates.
ERY-R, erythromycin A resistant (MIC ≥ 1.0 mg/L); PEN-R, penicillin G resistant (MIC ≥ 2.0 mg/L).

moniae infections. For infections caused by *H. influenzae*, rates of satisfactory clinical outcome were slightly lower (6/8) among strains with telithromycin MICs ≥ 8 mg/L.

Among patients in the PP population with pneumococcal bacteraemia, clinical cure and eradication rates were both 91.5% (43/47) for telithromycin. Those infected with penicillin G- and/or macrolide (erythromycin A)-resistant strains both achieved clinical cure and eradication rates of 7/9 (77.8%). The four cases with pneumococcal bacteraemia which were assessed as clinical failures at the post-therapy, test-of-cure visit included two patients switched to another antibiotic before blood cultures were repeated and one patient from whom penicillin G- and erythromycin A-resistant *S. pneumoniae* was eradicated (the case was deemed to be a clinical failure because of treatment with another antibiotic for urinary *Staph. aureus* infection). The remaining patient demonstrated persistence of infection with a penicillin G- and erythromycin A-resistant *S. pneumoniae* strain that was susceptible to telithromycin (MIC 0.12 mg/L). Thus, only one of the four pneumococcal bacteraemia clinical failures (all of which were resolved with subsequent antibacterial therapy) was a documented microbiological treatment failure.

Ten patients in the PP population treated with telithromycin had bacteraemia caused by organisms other than *S. pneumoniae* (one *B. cereus*, one *Staph. hyicus*, two *Staph. haemolyticus*, one *Streptococcus milleri*, one *Staphylococcus* spp. and four viridans group streptococci). All of these patients achieved clinical cure with presumed bacterial eradication.

DISCUSSION

Telithromycin is the first ketolide antibacterial agent to be approved for clinical use. The ketolides constitute a novel class within the macrolide–lincosamide–streptogramin$_B$ group of antibacterial agents. Telithromycin was specifically designed to provide optimal empirical therapy for community-acquired upper and lower RTIs. Its spectrum of antibacterial activity covers all relevant common respiratory pathogens, including isolates resistant to other antibacterials, and atypical or intracellular pathogens [46]. Compared with many antibacterial agents currently recommended for the treatment of such infections, telithromycin demonstrates high rates of clinical and bacteriological efficacy [15]. This was demonstrated in 13 phase III clinical trials, the results of which were pooled for the purpose of the present study.

As this was a pooled analysis of data from a number of open-label and comparator-controlled

clinical trials across four different indications, a formal statistical comparison of these data was not possible. However, a descriptive analytical approach was adopted to compare the pooled activity of telithromycin with that of comparators. Overall, our findings confirm high levels of susceptibility to telithromycin among all pathogens most commonly associated with community-acquired RTIs, supporting the potential utility of telithromycin as appropriate empirical therapy for RTI indications.

In total, 99.5% of *S. pneumoniae* isolates were susceptible to ≤1.0 mg/L telithromycin, and all were susceptible to ≤2.0 mg/L telithromycin, including penicillin G- and macrolide (erythromycin A)-resistant strains. This is an important finding, given the increasing prevalence of such resistance among pneumococci [5,6]. Telithromycin also provided good coverage against other major respiratory pathogens, including *M. catarrhalis* and *S. pyogenes*. High rates of clinical cure and bacteriological eradication (87.1% and 84.3%, respectively) were achieved among *H. influenzae* isolates, even for those isolates that had a telithromycin MIC as high as 4.0 mg/L (95.1% and 92.7%, respectively). While it must be accepted that the number of isolates for which the telithromycin MIC equalled 4.0 mg/L was relatively small ($n = 41$), the apparent success of telithromycin against strains of *H. influenzae* with intermediate susceptibility may be explained in part by pharmacokinetic and pharmacodynamic parameters. Telithromycin demonstrates concentration-dependent bactericidal activity against key respiratory pathogens, including *S. pneumoniae*, *M. catarrhalis* and *H. influenzae* [47,48]. Furthermore, Drusano *et al.* [49] found that CAP patients, from whom organisms with telithromycin MICs as high as 4 mg/L (including *H. influenzae*) were isolated, had a high probability of success with telithromycin treatment. In the present study, clinical cure and eradication rates for telithromycin were slightly lower for strains of *H. influenzae* with MICs ≥8 mg/L, although the number of such isolates was very small ($n = 8$). Azithromycin, which has similar pharmacokinetic and pharmacodynamic properties to telithromycin, has breakpoints of ≤4, 8 and ≥16 mg/L, respectively, for susceptible, intermediate and resistant isolates of *H. influenzae*. Based on these data and new data from clinical trials conducted since the original phase III studies, breakpoints of ≤4, 8 and ≥16 mg/L for telithromycin against *H. influenzae* have been approved by the subcommittee of the National Committee for Clinical Laboratory Standards (Aventis Pharmaceuticals, personal communication). Applying a susceptibility breakpoint of ≤4 mg/L to the isolates of *H. influenzae* from respiratory or blood samples in this study would result in 95.6% (327/342) of isolates being classified as susceptible to telithromycin (see Table 4). Overall, the results therefore suggest that empirical therapy with telithromycin may well achieve clinical and bacteriological success for those infections caused by *H. influenzae*, although further clinical experience with this agent is required to confirm this conclusion.

It is well established that bacteraemia is a serious complication of community-acquired RTIs such as CAP and AECB. Thus, for pneumococcal pneumonia, bacteraemia occurs in up to 30% of patients and increases the risk of mortality by up to 5.2-fold [50]. In the present study, 47 patients with pneumococcal bacteraemia were identified in the PP population, including a minor proportion infected with penicillin G- and macrolide (erythromycin A)-resistant strains. Overall, treatment with telithromycin was associated with high rates of clinical and bacteriological efficacy in these at-risk patients (91.5% and 91.5%, respectively). Telithromycin displays concentration-dependent killing, and its AUC/MIC ratio has been shown to be the pharmacodynamic and pharmacokinetic variable that best predicts outcome [51]. In addition, pharmacokinetic studies have demonstrated that, following oral administration, telithromycin achieves plasma concentrations adequate to maintain activity against key respiratory pathogens throughout the dosing period [52]. These factors may account for its activity against invasive isolates, and are important properties for any oral agent intended for the empirical treatment of community-acquired RTIs.

The comparator antibacterials used in the phase III clinical trials of telithromycin were generally given as a 10-day course of therapy, with some agents requiring multiple daily administration. Several studies have demonstrated that such protracted courses of treatment, and/or the need to administer doses throughout the day, may be associated with reduced compliance, especially once the symptoms of the infection start to resolve [53–55]. A reduction in compliance can, in turn,

result in an increased risk of treatment failure and may encourage the emergence of drug-resistant organisms. The rates of clinical cure and satisfactory bacteriological outcome observed in the present analysis for a 5-day course of telithromycin were comparable to those observed for a 10-day course of this agent and other antibacterial agents. These results are similar to findings from an individual study of patients treated with 5- or 10-day courses of telithromycin for acute sinusitis [39]. A 5-day course of treatment with telithromycin 800 mg once-daily may therefore provide a short and reliable treatment regimen that potentially increases patients' adherence to the course of treatment.

In conclusion, telithromycin 800 mg once-daily appears to provide excellent coverage against clinical isolates of key respiratory pathogens, including those isolated from blood cultures and those resistant to either penicillin G or the macrolides (erythromycin A), with high rates of clinical cure and bacterial eradication. These results indicate that telithromycin should provide effective first-line empirical therapy for community-acquired upper and lower RTIs.

ACKNOWLEDGEMENTS

This study was financially supported by Aventis Pharmaceuticals, Bridgewater, NJ, USA. The findings of the study were presented in part at the 22nd International Congress on Chemotherapy, 30 June to 3 July 2001, Amsterdam, The Netherlands [abstract no. 17.040].

REFERENCES

1. Bartlett JG. IDCP guidelines: management of upper respiratory tract infections. *Infect Dis Clin Pract* 1997; **6**: 212–220.
2. Garau J, Burry B, Butzler J-P, Dagan R, Pelton SI. Upper respiratory tract infections: etiology, current treatment, and experience with fluoroquinolones. *Clin Microbiol Infect* 1998; **4**(suppl 2): 51–58.
3. Ball P. Acute exacerbations of chronic bronchitis: the clinical problem, patient profiles and recommendations (guidelines) for therapy. *J Infect Dis Antimicrob Agents* 1999; **6**: 41–48.
4. Bartlett JG, Dowell SF, Mandell LA, File TM, Musher DM, Fine AM. Practice guidelines for the management of community-acquired pneumonia in adults. *Clin Infect Dis* 2000; **31**: 347–382.
5. Thornsberry C, Ogilvie P, Kahn J, Mauriz Y. Surveillance of antimicrobial resistance in *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Moraxella catarrhalis* in the United States in the 1996–1997 respiratory season. *Diagn Microbiol Infect Dis* 1997; **29**: 249–257.
6. Felmingham D, Grüneberg RN, the Alexander Project Group. The Alexander Project 1996–1997: latest susceptibility data from this international study of bacterial pathogens from community-acquired lower respiratory tract infections. *J Antimicrob Chemother* 2000; **45**: 191–203.
7. Hsuch PR, Chen HM, Huang AY, Wu JJ. Decreased activity of erythromycin against *Streptococcus pyogenes* in Taiwan. *Antimicrob Agents Chemother* 1995; **39**: 2239–2242.
8. Jasir A, Schalen C. Survey of macrolide resistance phenotypes in Swedish clinical isolates of *Streptococcus pyogenes*. *J Antimicrob Chemother* 1998; **41**: 135–137.
9. Giovanetti E, Montanari MP, Marchetti F, Varaldo PE. *In vitro* activity of ketolides telithromycin and HMR 3004 against Italian isolates of *Streptococcus pyogenes* and *Streptococcus pneumoniae* with different erythromycin susceptibility. *J Antimicrob Chemother* 2000; **46**: 905–908.
10. Martin JM, Green M, Barbadora KA, Wald ER. Erythromycin-resistant group A streptococci in schoolchildren in Pittsburgh. *N Engl J Med* 2002; **346**: 1200–1206.
11. Reid R, Bradley JS, Hindler J. Pneumococcal meningitis during therapy of otitis media with clarithromycin. *Pediatr Infect Dis J* 1995; **14**: 1104–1105.
12. Fogarty C, Goldschmidt R, Bush K. Bacteremic pneumonia due to multidrug-resistant pneumococci in 3 patients treated unsuccessfully with azithromycin and successfully with levofloxacin. *Clin Infect Dis* 2000; **31**: 613–615.
13. Garau J. The clinical impact of macrolide resistance in pneumococcal respiratory infections. *Int J Antimicrob Agents* 2001; **18**(suppl 1): 33–38.
14. Kelley MA, Weber DJ, Gilligan P, Cohen MS. Breakthrough pneumococcal bacteremia in patients being treated with azithromycin and clarithromycin. *Clin Infect Dis* 2000; **31**: 1008–1011.
15. Barman Balfour JA, Figgitt DP. Telithromycin. *Drugs* 2001; **61**: 815–829.
16. Agouridas C, Bonnefoy A, Chantot JF. *In vitro* antibacterial activity of HMR 3647, a novel ketolide highly active against respiratory pathogens [abstract 1.11]. In: *Abstracts of the 4th International Conference on the Macrolides, Azalides, Streptogramins and Ketolides, Barcelona, Spain.* 1998.
17. Barry AL, Fuchs PC, Brown SD. *In vitro* activities of the ketolide HMR 3647 against recent Gram-positive clinical isolates and *Haemophilus influenzae*. *Antimicrob Agents Chemother* 1998; **42**: 2138–2140.
18. Pankuch GA, Visalli MA, Jacobs MR, Appelbaum PC. Susceptibilities of penicillin- and erythromycin-susceptible and -resistant pneumococci to HMR 3647 (RU 66647), a new ketolide, compared with susceptibilities to 17 other agents. *Antimicrob Agents Chemother* 1998; **42**: 624–630.
19. Pankuch GA, Hoellman DB, Lin G, Bajaksouzian S, Jacobs MR, Appelbaum PC. Activity of HMR 3647 compared to those of five agents against *Haemophilus influenzae* and *Moraxella catarrhalis* by MIC determination and time–kill assay. *Antimicrob Agents Chemother* 1998; **42**: 3032–3034.
20. Reinert RR, Bryskier A, Lütticken R. *In vitro* activities of the new ketolide antibiotics HMR 3004 and HMR 3647 against *Streptococcus pneumoniae* in Germany. *Antimicrob Agents Chemother* 1998; **42**: 1509–1511.
21. Betriu C, Gomez M, Redondo M, Sanchez A, Palau ML, Picazo JJ. *In vitro* activity of the ketolide HMR 3647 against *Streptococcus pyogenes* [abstract 1250]. In: *Program and abstracts of the 39th Interscience Conference on Antimicrobial*

Agents and Chemotherapy, San Francisco, CA. Washington, DC: American Society for Microbiology, 1999; 260.
22. Hoban DJ, Zhanel GG, Karlowsky JA. *In vitro* activity of the novel ketolide HMR 3647 and comparative oral antibiotics against Canadian respiratory tract isolates of *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis*. *Diagn Microbiol Infect Dis* 1999; **35**: 37–44.
23. Wootton M, Bowker KE, Janowska A, Holt HA, MacGowan AP. *In-vitro* activity of HMR 3647 against *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis* and beta-hemolytic streptococci. *J Antimicrob Chemother* 1999; **44**: 445–453.
24. Descheemaeker P, Chapelle S, Lammens C *et al*. Macrolide resistance and erythromycin resistance determinants among Belgian *Streptococcus pyogenes and Streptococcus pneumoniae* isolates. *J Antimicrob Chemother* 2000; **45**: 167–173.
25. Giovanetti E, Montanari MP, Marchetti F, Varaldo PE. *In vitro* activity of the ketolides telithromycin and HMR 3004 against Italian isolates of *Streptococcus pyogenes* and *Streptococcus pneumoniae* with different erythromycin susceptibility. *J Antimicrob Chemother* 2000; **46**: 905–908.
26. Dubois J, St Pierre C. *In vitro* activity of telithromycin, macrolides and quinolones against respiratory tract pathogens [abstract 2152]. In: *Program and abstracts of the 40th Interscience Conference on Antimicrobial Agents and Chemotherapy, Toronto, Canada*. Washington, DC: American Society for Microbiology, 2000; 178.
27. Roblin PM, Hammerschlag MR. *In vitro* activity of a new ketolide antibiotic, HMR 3647, against *Chlamydia pneumoniae*. *Antimicrob Agents Chemother* 1998; **42**: 1515–1516.
28. Schülin T, Wennersten CB, Ferraro MJ, Moellering RC, Eliopoulos GM. Susceptibilities of *Legionella* spp. to newer antimicrobials *in vitro*. *Antimicrob Agents Chemother* 1998; **42**: 1520–1523.
29. Bébéar CM, Renaudin H, Bryskier A, Bébéar C. Comparative activities of telithromycin (HMR 3647), levofloxacin and other antimicrobial agents against human mycoplasmas. *Antimicrob Agents Chemother* 2000; **44**: 1980–1982.
30. Rastogi N, Goh KS, Berchel M, Bryskier A. *In vitro* activities of the ketolides telithromycin (HMR 3647) and HMR 3004 compared to those of clarithromycin against slowly growing mycobacteria at pHs 6.8 and 7.4. *Antimicrob Agents Chemother* 2000; **44**: 2848–2852.
31. Hammerschlag MR. Community-acquired pneumonia due to atypical organisms in adults: diagnosis and treatment. *Infect Dis Clin Pract* 1999; **8**: 232–240.
32. Davies TA, Dewasse BE, Jacobs MR, Appelbaum PC. *In vitro* development of resistance to telithromycin (HMR 3647), four macrolides, clindamycin, and pristinamycin in *Streptococcus pneumoniae*. *Antimicrob Agents Chemother* 2000; **44**: 414–417.
33. Leclercq R. Safeguarding future antimicrobial options: strategies to minimize resistance. *Clin Microbiol Infect* 2001; **7**(suppl 3): 18–23.
34. Buchanan P, McNeil D, Tady D, Andrade C, Leroy B. A 5-day course of telithromycin, the first ketolide antimicrobial, is as effective as 10 days' cefuroxime axetil in the treatment of acute maxillary sinusitis [abstract 910]. In: *Program and abstracts of the 41st Interscience Conference on Antimicrobial Agents and Chemotherapy, Chicago, IL.* Washington, DC: American Society for Microbiology, 2001; 461.
35. Aubier M, Aldons PM, Leak A *et al*. Telithromycin is as effective as amoxicillin/clavulanate in acute exacerbations of chronic bronchitis. *Respir Med* 2002; **96**: 862–871.
36. Carbon C, Moola S, Velancsics I, Leroy B, Rangaraju M, Decosta P. Telithromycin 800 mg once daily for seven to ten days is an effective and well tolerated treatment for community-acquired pneumonia. *Clin Microbiol Infect* 2003; **9**: 691–703.
37. Hagberg L, Torres A, van Rensburg D, Rangaraju M, Ruuth E. Efficacy and tolerability of once-daily telithromycin compared with high-dose amoxicillin for treatment of community-acquired pneumonia. *Infection* 2002; **30**: 378–386.
38. Norrby SR, Rabie W, Bacart P *et al*. Efficacy of short-course therapy with the ketolide telithromycin compared with 10 days' penicillin V in the treatment of pharyngitis/tonsillitis. *Scand J Infect Dis* 2001; **33**: 883–890.
39. Roos K, Brunswig-Pitschner C, Kostrica R *et al*. Efficacy and tolerability of once-daily therapy with telithromycin for 5 or 10 days for the treatment of acute maxillary sinusitis. *Chemotherapy* 2002; **48**: 100–108.
40. Tellier G, Hassman J, Leroy B, Sidarous E, Youngblood D. Oral telithromycin (HMR 3647; 800 mg od) is well tolerated and as effective as oral clarithromycin (500 mg bid) in community-acquired pneumonia (CAP) in adults [abstract 2227]. In: *Abstracts of the 40th Interscience Conference on Antimicrobial Agents and Chemotherapy,* Toronto, Canada. Washington, DC: American Society for Microbiology 2000; **471**.
41. Fogarty C, Patel TC, Galbraith H, Zuberbuhler GA, Leroy B. Efficacy and safety of telithromycin 800 mg once daily in pneumococcal community-acquired pneumonia [abstract L-857]. In: *Program and abstracts of the 41st Interscience Conference on Antimicrobial Agents and Chemotherapy, Chicago, IL.* Washington, DC: American Society for Microbiology, 2001; 449.
42. Quinn J, Ruoff JE, Ziter PS. Efficacy and tolerability of 5-day, once-daily telithromycin compared with 10-day, twice-daily clarithromycin for the treatment of group A beta-hemolytic streptococcal tonsillitis/pharyngitis: a multicenter, randomized, double-blind, parallel group study. *Clin Ther* 2003; **25**: 422–443.
43. van Rensburg DJ, Matthews PA, Leroy B. Efficacy and safety of telithromycin in community-acquired pneumonia. *Curr Med Res Opin* 2002; **18**: 397–400.
44. National Committee for Clinical Laboratory Standards. *Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically*. NCCLS publication no. M7-A4. Wayne, PA: NCCLS, 1997.
45. Sutcliffe J, Grebe T, Tait-Kamradt A, Wondrack L. Detection of erythromycin-resistant determinants by PCR. *Antimicrob Agents Chemother* 1996; **40**: 2562–2566.
46. Felmingham D. Microbiological profile of telithromycin, the first ketolide antimicrobial. *Clin Microbiol Infect* 2001; **7**(suppl 3): 2–10.
47. Felmingham D, Clark S, Robbins MJ, Dencer C, Bryskier A. In vitro bactericidal activity of HMR 3647 against respiratory tract pathogens [Poster E-133]. In: *38th Interscience Conference on Antimicrobial Agents and Chemotherapy, San Diego, CA.* Washington DC: American Society for Microbiology, 1998; 207.
48. Otsuki M, Harada H, Nishino T. In vitro antibacterial activity of HMR 3647, a new ketolide antibiotic [abstract

E-137]. In: *Program and abstracts of the 38th Interscience Conference on Antimicrobial Agents and Chemotherapy, San Diego, CA.* Washington, DC: American Society for Microbiology, 1998; 208.
49. Drusano GL, Preston SL, Decosta P, Rangaraju M, Leroy B. Pharmacokinetics (PK) and pharmacodynamics (PD) of telithromycin in the treatment of community-acquired pneumonia (CAP) [abstract 1388]. In: *Program and abstracts of the 41st Interscience Conference on Antimicrobial Agents and Chemotherapy, Chicago, IL.* Washington, DC: American Society for Microbiology, 2001; 36.
50. Fine MJ, Smith MA, Carson CA *et al.* Prognosis and outcomes of patients with community-acquired pneumonia. A meta-analysis. *JAMA* 1996; **275**: 134–141.
51. Nicolau DP. Predicting antibacterial response from pharmacodynamic and pharmacokinetic profiles. *Infection* 2001; **29**(suppl 2): 11–15.
52. Namour F, Wessels DH, Pascual MH, Reynolds D, Sultan E, Lenfant B. Pharmacokinetics of the new ketolide telithromycin (HMR 3647) administered in ascending single and multiple doses. *Antimicrob Agents Chemother* 2001; **45**: 170–175.
53. Eisen SA, Miller DK, Woodward RS, Spitznagel E, Prybeck TR. The effect of prescribed daily dose frequency on patient medication compliance. *Arch Intern Med* 1990; **150**: 1881–1884.
54. Sclar DA, Tartaglione TA, Fine MJ. Overview of issues related to medical compliance with implications for the outpatient management of infectious diseases. *Infect Agents Dis* 1994; **3**: 266–273.
55. Al-Shammari SA, Khoja T, Al-Yamani MJ. Compliance with short-term antibiotic therapy among patients attending primary health centres in Riyadh, Saudi Arabia. *J R Soc Health* 1995; **115**: 231–234.